Complete Summary

GUIDELINE TITLE

Evidence based clinical practice guideline for fever of uncertain source in infants 60 days of age or less.

BIBLIOGRAPHIC SOURCE(S)

Cincinnati Children's Hospital Medical Center. Evidence based clinical practice guideline for fever of uncertain source in infants 60 days of age or less. Cincinnati (OH): Cincinnati Children's Hospital Medical Center; 2003 Jun. 12 p. [49 references]

COMPLETE SUMMARY CONTENT

SCOPE

DISEASE/CONDITION(S)

Fever of uncertain source

GUIDELINE CATEGORY

Diagnosis
Evaluation
Management
Risk Assessment

CLINICAL SPECIALTY

Emergency Medicine
Family Practice
Infectious Diseases
Pediatrics

INTENDED USERS

Advanced Practice Nurses
Health Care Providers
Nurses
Physician Assistants
Physicians

GUIDELINE OBJECTIVE(S)

To improve the use of appropriate laboratory studies, the use of appropriate antibiotic therapy, the efficiency of care, and parental satisfaction and understanding of family-centered care in the target population

TARGET POPULATION

Infants, 60 days of age or less, presenting as outpatients with a fever of uncertain source

These guidelines are not intended to be used in the following:

- Patients with underlying disorders that affect their immunity or might otherwise increase their risk for serious bacterial or viral infections
- Child on current antibiotic therapy
- Child given diphtheria, tetanus, and acellular pertussis (DTaP) immunization within 48 hours
- Child presenting with seizures
- Child requiring intensive care management

INTERVENTIONS AND PRACTICES CONSIDERED

Diagnostic/Risk Assessment

1. Clinical assessment, including rectal temperatures, history, and physical examination
2. Laboratory studies, including complete blood count (CBC) with differential, blood culture, urinalysis, urine culture, lumbar puncture, stool culture, viral cultures, chest x-rays, evaluation for neonatal herpes simplex virus infections, polymerase chain reaction (PCR) for enterovirus and human herpes virus-6 (HHV-6), and rapid plasma reagin (RPR) test
3. Decision to admit to hospital or maintain outpatient care based on risk factors identified by clinical assessment or diagnostic testing, clinical judgment, and needs of family

Management/Treatment

1. Antibiotics for presumed serious bacterial infection
    - Ampicillin sodium
    - Cefotaxime (Clarforan)
    - Ceftriaxone (Rocephin)
    - Gentamicin

    - Nafcillin
2. Antiviral (acyclovir) for presumed neonatal herpes simplex virus (HSV) infection
3. Nutrition (diet for age, as tolerated, and supplemental hydration, as required)
4. Infection control
5. Consults and referrals
6. Education of family
7. Discharge criteria

MAJOR OUTCOMES CONSIDERED

- Risk for serious bacterial infection (SBI)
- Sensitivity, specificity, and diagnostic value of clinical assessments and diagnostic tests
- Risk for herpes simplex viral (HSV) infection

METHODOLOGY

METHODS USED TO COLLECT/SELECT EVIDENCE

Searches of Electronic Databases
Searches of Patient Registry Data

DESCRIPTION OF METHODS USED TO COLLECT/SELECT THE EVIDENCE

Not stated

NUMBER OF SOURCE DOCUMENTS

Not stated

METHODS USED TO ASSESS THE QUALITY AND STRENGTH OF THE EVIDENCE

Not stated

RATING SCHEME FOR THE STRENGTH OF THE EVIDENCE

Not applicable

METHODS USED TO ANALYZE THE EVIDENCE

Systematic Review

DESCRIPTION OF THE METHODS USED TO ANALYZE THE EVIDENCE

Not stated

METHODS USED TO FORMULATE THE RECOMMENDATIONS

Expert Consensus

DESCRIPTION OF METHODS USED TO FORMULATE THE RECOMMENDATIONS

The recommendations contained in this guideline were formulated by an interdisciplinary working group, which performed systematic and critical literature reviews using a grading scale and examined current local clinical practices.

During formulation of these guidelines, the team members have remained cognizant of current controversies and disagreements over the management of these patients. They have tried to resolve controversial issues by consensus where possible and, when not possible, to offer optional approaches to care in the form of information that includes best supporting evidence of efficacy for alternative choices.

RATING SCHEME FOR THE STRENGTH OF THE RECOMMENDATIONS

Not applicable

COST ANALYSIS

A formal cost analysis was not performed and published cost analyses were not reviewed.

METHOD OF GUIDELINE VALIDATION

Internal Peer Review

DESCRIPTION OF METHOD OF GUIDELINE VALIDATION

The guidelines have been reviewed and approved by clinical experts not involved in the development process, senior management, Risk Management & Corporate Compliance, the Institutional Review Board, other appropriate hospital committees, and other individuals as appropriate to their intended purposes.

RECOMMENDATIONS

MAJOR RECOMMENDATIONS

Each recommendation is followed by evidence grades (A-X) identifying the type of supporting evidence. Definitions of the evidence grades are presented at the end of the Major Recommendations field.

Clinical Assessment

1. It is recommended that rectal temperatures are preferred to axillary or other temperature measures (Center for Reviews and Dissemination Reviewers, 1996 [M]; Hooker, 1993 [C]; Reisinger, Kao, & Grant, 1979 [C]).

Note 1: A parental report of fever detected only by touch is likely to be accurate (sensitivity 82--89%, specificity 76--86%) (Graneto & Soglin, 1996 [C]; Hooker et al., 1996 [C]; Singhi & Sood, 1990 [C]).

Note 2: The magnitude of fever may not be useful for predicting illness source or severity (Bonadio et al., 1991 [C]; Kluger, 1992 [S]).

2. It is recommended and essential that a thorough history and physical examination be performed. In the history and the physical examination it is important to elicit high risk clinical elements. See Table 1 below for points of consideration.

Table 1: Definitions (Baraff et al.,1993 [E]) unless otherwise specified

Fever

Rectal temperature $\geq$38ºC (100.4ºF) (Bonadio, Smith, & Sabnis, 1994 [D])

Fever of Uncertain Source (FUS)

An acute febrile illness in which the etiology of the fever is not apparent after a thorough history and physical exam

Serious Bacterial Infection (SBI)

- Meningitis
- Bone and joint infections
- Soft tissue infections (cellulitis)
- Pneumonia
- Urinary tract infections (UTI)
- Sepsis/bacteremia
- Enteritis

Toxic Appearance -- "Yale Observation Scale" (for study population <24 months of age); see also (Baker, Bell, & Avner, 1993 [A]; McCarthy et al., 1982 [C])

- Lethargy
- Poor or absent eye contact
- Failure of child to recognize parents or failure to interact with persons or objects in the environment
- Poor perfusion of the extremities
- Acrocyanosis
- Mottling
- Slow capillary refill time of >2 seconds in "warm" environment (Gorelick, Shaw, & Baker, 1993 [C]; Schriger & Baraff, 1988 [C])
- Hyperventilation or marked hypoventilation or cyanosis

Low Risk for SBI -- "Rochester Criteria"; see also (Baker, Bell, & Avner, 1993 [A]; Jaskiewicz et al., 1994 [C]; McCarthy et al., 1982 [C])

- Prior history of being healthy
    - born at term (≥37 weeks gestation)
    - has not been previously hospitalized
    - has no chronic or underlying illness
    - was not hospitalized longer than mother
    - was not treated for unexplained hyperbilirubinemia
    - has not received and was not receiving antimicrobial agents
    - no intrapartum history of mother for fever, Group B streptococcus, or antibiotic treatment
- No focal bacterial infection on physical exam
- No evidence of purulent otitis media, skin or soft tissue infection, or bone or joint skeletal infection
- Negative laboratory screen

Laboratory Studies

1. It is recommended that the following five laboratory tests be performed in all infants with FUS (Klassen & Rowe, 1992 [M]; Jaskiewicz et al., 1994 [C]; Dagan et al., 1988 [C]; Dagan et al., 1985 [C]; Kadish et al., 2000 [D]; Baraff et al., 1993 [E]).
    A. Complete blood count (CBC) with differential

        Note 1: An abnormal CBC is defined as: white blood cells (WBC) >15,000/microliter or <5,000/microliter; WBC band forms >1,500/microliter (Dagan et al., 1988 [C]; Dagan et al., 1985 [C]; Bonadio, Smith, & Carmody, 1992 [D]).

        Note 2: WBC lab values have no predictive value in determining the risk of meningitis (Bonsu & Harper, 2003 [Q]).

        Note 3: A band-to-neutrophil ratio <0.2 improves the negative predictive value for SBI to 98% or greater when added to the screening criteria (Baker, Bell, & Avner, 1993 [A]).

    B. Blood culture
    C. Urinalysis (Herr et al., 2001 [D])

        Note 1: Abnormal microscopy defined as spun urine >10 WBC/high-power field (hpf).

        Note 2: Gram stain of sample for organisms is more sensitive (94%) and specific (92%) than simple urinalysis or "dip sticks" as quick indicator of infection (Lockhart et al., 1995 [C]).

    D. Urine culture

        It is recommended that urine samples be collected by catheter, as they are less likely to be contaminated than "clean catch" urine samples (Weinberg & Gan, 1991 [D]).

    E. Lumbar puncture (LP)

- It is recommended that all infants receive a lumbar puncture.
- Exception: In infants 31 to 60 days AND with the presence of all of the following, delaying or omitting a lumbar puncture may be considered (Jaskiewicz et al.,1994 [C]; Dagan et al., 1988 [C]; Local Expert Consensus [E]):
    - Low risk as identified with strict screening criteria utilizing both clinical assessment and diagnostic testing (see Table 1 above and in the original guideline document)
    - Available reliable follow-up in 12 to 24 hours
    - Healthcare provider(s) confident that parent will use appropriate observational and follow-up skills
    - Primary care physician (PCP) and family agree with plan of care
    - Antibiotic therapy will not be initiated
- It is recognized that an acceptable cerebrospinal fluid (CSF) specimen might not be obtained secondary to failed procedure, traumatic lumbar puncture, or parental refusal. If the decision to start antibiotics has already been made, then it is recommended that treatment be initiated (Local Expert Consensus [E]).

2. It is recommended that the following also be considered:
    - Stool culture (if child has diarrhea)
    - Viral cultures in selected patients and as appropriate to season
    - Chest x-ray (if respiratory signs)
3. A. For infants 0 to 30 days with FUS, it is recommended that a laboratory evaluation for neonatal herpes simplex virus (HSV) infections be considered:
    - If risk factor(s) are present (see Appendix in the guideline document), or
    - If the patient is not improving on antibiotic therapy (Local Expert Consensus [E])

    The following laboratory tests are recommended if an evaluation for neonatal HSV infection is performed.

    - Blood viral culture
    - CSF viral culture
    - CSF polymerase chain reaction (PCR)
    - Conjunctiva viral culture
    - Skin lesion viral culture
    - Nasopharyngeal (NP) viral culture
    - Rectal viral culture
    - Also consider
        - Chest x-ray
        - Liver function studies

    B. For infants 31 to 60 days with FUS, it is recommended that laboratory evaluation for neonatal HSV infections be reserved primarily for those with clinical findings suggestive of an HSV infection or a prior history of HSV.

    Note: In the infant beyond one month of age there is a considerably reduced risk for neonatal HSV infection; 95 to

98% present prior to 22 days of age (Koskiniemi et al., 1989 [D]; Sullivan-Bolyai et al.,1986 [D]).

See Appendix in the original guideline document) for information which may help when deciding on the appropriateness of evaluating for and treating neonatal HSV infections.

4. It is recommended that the following laboratory tests be considered selectively in non-low-risk infants:
    - PCR. A positive PCR does not rule out SBI. Consider applicable specificity, sensitivity and turnaround time for specific PCR at the time of testing (Local Expert Consensus [E]).
        - Enterovirus (summer and fall). At present, test results are available within 24 hours.

          Note 1: CSF and blood sources for PCR are the most sensitive for diagnosis of enterovirus infection (Byington et al., 1999 [C]; Rotbart et al.,1999 [C]).

          Note 2: PCR is more sensitive than viral culture in detecting enterovirus (Rotbart et al., 1999 [C]).

        - Human herpes virus 6 (HHV-6) (Byington et al., 2002 [C])
    - Rapid plasma reagin (RPR)

Admission Criteria

1. It is recommended that all infants 0 to 30 days of age with FUS be hospitalized (Kadish et al., 2000 [D]).

   Note: 3.2 to 3.5% of febrile infants 0 to 30 days identified as low-risk [by the Philadelphia or Boston protocols] will have SBI (Kadish et al., 2000 [D]).

2. It is recommended that any infant 31 to 60 days of age with FUS identified as high-risk clinically or by laboratory data be hospitalized (Baraff et al., 1993 [E]).
3. It is recommended that low-risk infants 31 to 60 days may be managed as outpatients or inpatients (Baker, Bell, & Avner, 1993 [A]; Baker, Bell, & Avner, 1999 [C]; Baskin, O´Rourke, & Fleisher, 1992 [C]; Dagan et al., 1988 [C]; Wasserman & White, 1990 [D]). This decision must take into consideration:
    - The needs of the family
    - The judgment of the primary care physician
    - Excellent outpatient follow-up
    - Excellent communication with care provider as an outpatient assured.

      Note: Low-risk infants may be identified using strict screening criteria utilizing both clinical assessment and diagnostic testing. Use of these criteria has 98.9 to 100% negative predictive value for SBI (Baker, Bell, & Avner, 1993 [A]; Jaskiewicz et al.; 1994 [C], Herr et al.; 2001 [D]).

Medications

Antibiotics

1. It is recommended that all infants 0 to 30 days with FUS be treated with intravenous ampicillin plus a 3rd generation cephalosporin or gentamicin.

   Note: About 138 such infants need to be treated with ampicillin to prevent one case of Listeria monocytogenes or enterococcal infection (number needed to treat [NNT] = 138) (Brown, Burns, & Cummings, 2002 [M]).

2. Recommendations for treatment of infants 31 to 60 with FUS vary depending on laboratory and clinical findings.
   - It is recommended that the first line treatment for this group is intravenous 3rd generation cephalosporin alone (Byington et al., 2003 [D]; Sadow, Derr, & Teach, 1999 [D]).
   - It is recommended that intravenous ampicillin be considered as an addition to the antibiotic regimen for febrile infants 31 to 60 days in severely ill infants or with findings suggestive of UTI to assure coverage for rare organisms such as L. monocytogenes, gram-positive cocci, or enterococcus (Brown, Burns, & Cummings, 2002 [M]; Byington et al., 2003 [D]; Sadow, Derr, & Teach, 1999 [D]).

     Note: About 527 infants 31 to 60 days with FUS need to be treated with ampicillin to prevent one case of L. monocytogenes or enterococcal infection (number needed to treat = 527) (Brown, Burns, & Cummings, 2002 [M]).

   - Inpatient and outpatient low-risk infants may be managed without antibiotics pending culture results and/or a change in clinical status (Baker, Bell, & Avner, 1993 [A]; Baker, Bell & Avner, 1999 [C]; Jaskiewicz et al., 1994 [C]; Dagan et al.,1988 [C]).
   - It is recommended that those infants managed as outpatients and treated with antibiotics receive parenteral ceftriaxone (Baskin et al., 1992 [C]).

   See Table 2 in the original guideline document for summary of recommended doses for antibiotics.

3. It is recommended that the duration of initial antibiotic therapies cover a treatment period of 24 to 48 hours with discontinuance or continuation of therapy based on result of cultures or other tests and review of history and clinical response.

   Cultures must be checked after a true minimum incubation period of 36 hours, which begins when the inoculated culture is placed in the incubator.

   Note 1: The probability of identifying SBI in febrile infants (28--90 days) after 24 hours is about 1.1% among all patients and 0.3% among low risk patients (Kaplan et al., 2000 [D]).

Note 2: In blood cultures of infants 0 to 6 months, mean time to positivity for true pathogens is about 17.5 hours and for contaminants is about 27.9 hours (McGowan, Foster, & Coffin, 2000 [C]). Median times to positivity for urine and CSF cultures are 16 and 18 hours, respectively, in febrile infants 28 to 90 days (Kaplan et al., 2000 [D]).

Antiviral

1. It is recommended that acyclovir not be added routinely to standard antimicrobial therapy for infants with FUS. Benefit is moderated by the rarity of neonatal HSV infection, especially with an FUS presentation, and drug therapy is not without risk (Local Expert Consensus [E]).
2. Acyclovir is recommended when the decision is made to initiate therapy for the treatment of possible neonatal HSV infection. Appropriate diagnostic specimens must be collected before therapy is initiated (Kimberlin et al.,2001 [C]).

See Table 2 in the original guideline document for recommended doses.

Nutrition

1. Diet for age as tolerated
2. Supplemental hydration as required. This is especially recommended for <1-week-old breastfeeding infant with decreased urine output if on drugs (e.g., acyclovir) that are dependent on good renal function for excretion.

Infection Control

Follow infection control precautions (droplet, contact, or standard) as appropriate to presumptive diagnosis.

Consults and Referrals

Consider consult with Infectious Diseases if:

1. Diagnosis or clinical course of infection is unusual
2. There are questions regarding continuation or discontinuation of acyclovir in situations where neither the cultures nor the PCR are positive for HSV; or
3. HSV culture or HSV PCR results are positive

Education

Family education and review is recommended on the following topics.

A. Fever:
    - Observing signs, including taking an accurate temperature measurement
    - Causes
    - Therapies
B. Indications to call their physician
C. Anticipated course of the illness

(O'Neill-Murphy, Liebman, & Barnsteiner, 2001 [O])

Discharge Criteria

(Note: Begin discharge planning on admission.)

1. Well-appearing
2. Eating well
3. Antimicrobial therapies complete or can be continued in the home environment
4. Culture results negative when checked after a true minimum incubation period of 36 hours (which begins when the inoculated culture is placed in the incubator)
5. Hospitalized infant observed without antibacterial treatment is well-appearing at 24 hours
6. Family:
    - Has participated in the discharge planning and decision processes
    - Understands and agrees to any prescribed therapies or follow-up needs
    - Is confident in ability to care for infant at home
7. Home environment considered appropriate for continuing care prescriptions
8. Follow-up physician:
    - Is identified
    - Has participated in generating the discharge plan
    - Agrees with the discharge plan

Definitions:

Evidence Based Grading Scale:

A: Randomized controlled trial: large sample
B: Randomized controlled trial: small sample
C: Prospective trial or large case series
D: Retrospective analysis
E: Expert opinion or consensus
F: Basic laboratory research
S: Review article
M: Meta-analysis
Q: Decision analysis
L: Legal requirement
O: Other evidence
X: No evidence

CLINICAL ALGORITHM(S)

Clinical algorithms are provided in the original guideline document for:

- Managing Fever of Uncertain Source in Infants Age 0-60 Days
- Serious Bacterial Infection (SBI) Risk Assessment

EVIDENCE SUPPORTING THE RECOMMENDATIONS

REFERENCES SUPPORTING THE RECOMMENDATIONS

References open in a new window

TYPE OF EVIDENCE SUPPORTING THE RECOMMENDATIONS

The type of evidence is identified and classified for each recommendation (see "Major Recommendations").

Evidence Based Grading Scale:

A: Randomized controlled trial: large sample
B: Randomized controlled trial: small sample
C: Prospective trial or large case series
D: Retrospective analysis
E: Expert opinion or consensus
F: Basic laboratory research
S: Review article
M: Meta-analysis
Q: Decision analysis
L: Legal requirement
O: Other evidence
X: No evidence

BENEFITS/HARMS OF IMPLEMENTING THE GUIDELINE RECOMMENDATIONS

POTENTIAL BENEFITS

- Effective medical management of fever of uncertain source in infants 60 days of age or less
- Reduction of unnecessary variances in care without inhibiting care variances that might be beneficial for individual patients

POTENTIAL HARMS

Not stated

QUALIFYING STATEMENTS

QUALIFYING STATEMENTS

These recommendations result from review of literature and practices current at the time of their formulations. This protocol does not preclude using care modalities proven efficacious in studies published subsequent to the current revision of this document. The guideline document is not intended to impose standards of care preventing selective variances from the guidelines to meet the specific and unique requirements of individual patients. Adherence to this pathway

is voluntary. The physician in light of the individual circumstances presented by the patient must make the ultimate judgment regarding the priority of any specific procedure.

IMPLEMENTATION OF THE GUIDELINE

DESCRIPTION OF IMPLEMENTATION STRATEGY

Appropriate companion documents have been developed to assist in the effective dissemination and implementation of the guideline.

INSTITUTE OF MEDICINE (IOM) NATIONAL HEALTHCARE QUALITY REPORT CATEGORIES

IOM CARE NEED

Getting Better

IOM DOMAIN

Effectiveness
Patient-centeredness

IDENTIFYING INFORMATION AND AVAILABILITY

BIBLIOGRAPHIC SOURCE(S)

Cincinnati Children's Hospital Medical Center. Evidence based clinical practice guideline for fever of uncertain source in infants 60 days of age or less. Cincinnati (OH): Cincinnati Children's Hospital Medical Center; 2003 Jun. 12 p. [49 references]

ADAPTATION

Not applicable: The guideline was not adapted from another source.

DATE RELEASED

1998 Sep 10 (revised 2003 Jun)

GUIDELINE DEVELOPER(S)

Cincinnati Children's Hospital Medical Center - Hospital/Medical Center

SOURCE(S) OF FUNDING

Cincinnati Children's Hospital Medical Center

GUIDELINE COMMITTEE

Fever 0 to 60 Days Team Members 2003

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FINANCIAL DISCLOSURES/CONFLICTS OF INTEREST

The guideline was developed without external funding. All Team Members and Clinical Effectiveness support staff listed have declared whether they have any conflict of interest.

GUIDELINE STATUS

This is the current release of the guideline.

This guideline updates a previous version: Cincinnati Children's Hospital Medical Center. Evidence based clinical protocol guideline for fever of uncertain source in infants 60 days of age or less. Cincinnati (OH): Cincinnati Children's Hospital Medical Center; 1998. 32 p.

GUIDELINE AVAILABILITY

Electronic copies: Available in Portable Document Format (PDF) from the Cincinnati Children's Hospital Medical Center Web site.

For information regarding the full-text guideline, print copies, or evidence based practice support services contact the Children's Hospital Medical Center Health Policy and Clinical Effectiveness Department at HPCEInfo@chmcc.org.

AVAILABILITY OF COMPANION DOCUMENTS

None available

PATIENT RESOURCES

The following is available:

- Fever of uncertain source. Cincinnati, OH: Cincinnati Children's Hospital Medical Center, 1999 (revised 2003 Sep). (Patient Education Pamphlet 1049).

Electronic copies: Available from the Cincinnati Children's Hospital Medical Center Web site.

NGC STATUS

This summary was completed by ECRI on September 1, 1998. The information was verified by the guideline developer on December 1, 1998. This summary was updated by ECRI on March 11, 2004.

COPYRIGHT STATEMENT

Date Modified: 11/8/2004